DEMJANOV REACTION WITH 1-METHYL-2-AMINOMETHYLPIPERIDINE

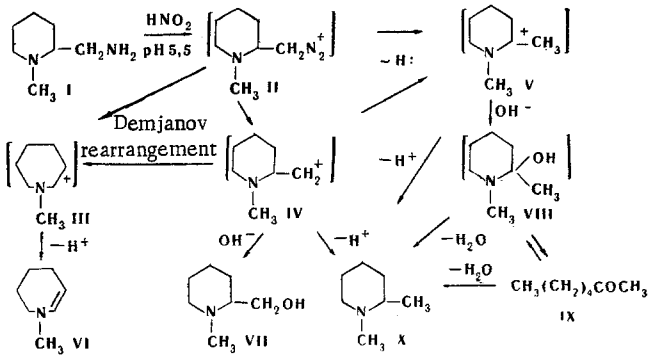
L. B. Dmitriev, I. I. Grandberg, and V. A. Moskalenko

UDC 547.822

The Demjanov rearrangement with ring expansion proceeds to a slight degree (~9%) during the deamination of 1-methyl-2-aminomethylpiperidine with nitrous acid, and the major reaction products are 1-methyl-2-hydroxymethylpiperidine and 6-methylamino-2-hexanone.

We have previously established that the Demjanov rearrangement proceeds to the extent of only 8% during the deamination of 1-methyl-3- and 1-methyl-4-aminomethylpiperidine [1,2]. It was of interest to study the behavior in this reaction of 1-methyl-2-aminomethylpiperidine which has a ring nitrogen close to the reaction center.

An investigation of the reaction products showed that only ~9% of the Demjanov rearrangement product (VI) is formed in this case.



As in the preceding cases, the chief processes are the formation of primary alcohol VII without rearrangement (49%) and hydride-ion migration with the formation of tertiary carbonium ion V, which, by reaction with the solvent, is converted to unstable tertiary alcohol VIII, which is then converted to amino ketone IX (16%). In addition, 26% of unsaturated compound X is formed, which may be the product of elimination of a hydrogen atom from primary carbonium ion IV or tertiary ion V, or may arise as a result of dehydration of amino ketone IX or its cyclic tautomer VIII during chromatography or directly during the deamination reaction.

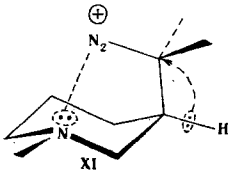
It should have been expected that the effect of the ring nitrogen atom would be similar to the effect of a hydroxyl group in the Tiffeneau–Demjanov reaction [3] and would promote the formation of a secondary carbonium ion (III) with ring expansion.

The deamination of 2-aminocyclohexanols [4], in which the nucleophilic group (OH), just as in 1-hydroxy-1-aminomethylcyclanes (Tiffeneau–Demjanov reaction), is in the β position relative to the amino

K. A. Timiryazev Moscow Agricultural Academy. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1654-1658, December, 1970. Original article submitted April 21, 1969.

group, indicates that when the orientation of these groups is fixed, the direction of migration is determined not so much by the properties of the nucleophilic group as by steric factors.

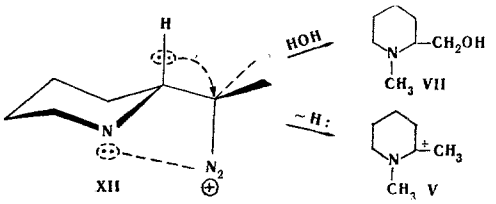
We previously [1,2] assumed that the diazonium methyl group is fixed during deamination of 1-methyl-3- and 1-methyl-4-aminomethyl piperidines due to the formation of a cyclic intermediate ion of the XI type, which is partially stabilized by interaction of the positive charge of the diazonium group with the unshared electron pair of the ring nitrogen atom.



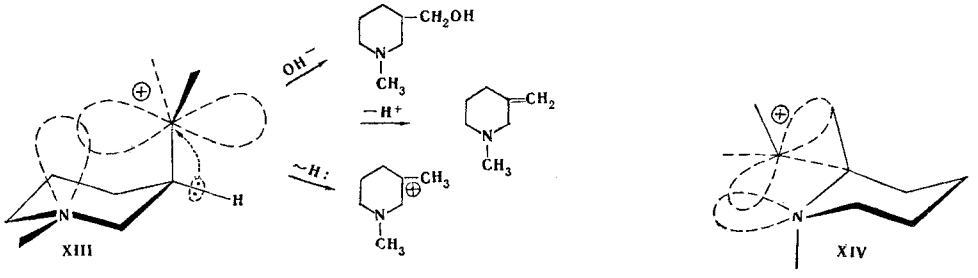
XI

For 1-methyl-2-aminomethylpiperidine it was also assumed that the unshared electron pair of the ring nitrogen atom may be the reason for intramolecular stabilization of the diazonium ion with the formation of an intermediate ion of the XII type.

In this case, during elimination of a nitrogen molecule one should expect the predominant migration of the hydrogen atom of the ring α-carbon atom in the trans position with respect to the diazo group with the formation of a tertiary carbonium ion (V).



Although the formation of an intermediate cyclic diazonium ion to a certain degree explains the predominant migration of a hydride ion rather than the migration of a ring carbon atom in the deamination of aminomethylpiperidines, it does not explain the formation of greater amounts of primary alcohols as compared with the deamination of aminomethylcarbocyclic compounds. From our point of view, it seems most likely that the predominance of the stabilization of the primary carbonium ion is due to interaction with solvent (H_2O) and migration of a hydrogen atom with the formation of a tertiary carbonium ion rather then migration of ring carbon atoms, leading to ring expansion, is determined by the conformation of the carbonium ion which, in turn, is determined by the intramolecular interaction of the free electron pair of the tertiary nitrogen atom of the ring with the free p orbital of the electron-deficient carbon atom. The unpaired electron pair of the ring nitrogen atom thus promotes intramolecular decomposition of the diazonium ion and by interacting with the free p orbital formed in the process, partially stabilizes the primary carbonium ion of the XIII type (for 1-methyl-3-aminomethylpiperidine) or of the XIV type (for 1-methyl-2-aminomethylpiperidine).



This sort of ion will apparently have a lower energy than the corresponding carbonium ion formed during the deamination of carbocyclic compounds. The interaction of this ion with solvent without rearrangement will therefore be more likely.

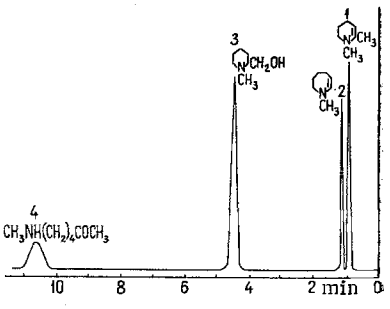


Fig. 1. Chromatogram of the products of deamination of 1-methyl-2-aminomethylpiperidine.

The ring hydrogen atom in intermediate cyclic ions XIII and XIV is also found in a position most favorable for migration, since it is in the trans position relative to the region of interaction of the free p orbital with the unshared electron pair of the ring nitrogen atom. In addition, the coplanar orientation of all four reaction centers in the case of 1-methyl-4-aminomethylpiperidine facilitates transfer of the migrating hydrogen atom, and, in the case of 1-methyl-3-aminomethylpiperidine and, probably, 1-methyl-2-aminomethylpiperidine, the noncoplanarity of the C–H bond with the plane of the free p orbital should probably hinder migration of the hydrogen atom. In fact, in contrast to the deamination of 1-methyl-4-aminomethylpiperidine, where apparently equal quantities of primary and tertiary alcohols (38 and 39%) are formed, in the second case, 62% and 49% of primary alcohols and only 14%of tertiary alcohol and 16%of amino ketone, respectively, are formed. One should apparently have a cautious attitude toward an estimate of the degree of hydride shift for compound I from only the amount of amino ketone IX since a portion of the tertiary carbonium ion (V) is probably converted to unsaturated X, directly or as a result of dehydration of its stabilization products (VIII and IX), both during the reaction and during chromatography.

The presence of relatively large amounts of amino ketone IX and X in the products of deamination of 1-methyl-2-aminomethylpiperidine compels us to assume that the significant gain in energy on passing from the primary carbonium center to the tertiary carbonium ion center makes possible the migration of a hydrogen atom to the conformation which is not the most favorable for such a migration.

1-Methyl-2-aminomethylpiperidine was deaminated under standard conditions [1]. An investigation of the products by means of gas-liquid chromatography [1] (Fig. 1) indicated that four compounds are formed in the reaction. These compounds were separated by preparative gas-liquid chromatography [1,2] for identification and establishment of their structures.

Catalytic hydrogenation of the mixture of compounds corresponding to peaks 1 and 2 in the chromatogram gave a mixture of 1,2,-dimethylpiperidine and 1-methylhexahydroazepine in the same quantitative ratio as the starting compounds. The structure of the hydrogenation products was proved by comparison of their retention times with the retention times of authentic samples.

The UV spectra of the unsaturated reaction products contained an absorption maximum (λ_{max}) at 231 nm (log ε 3.68) characteristic for Δ^2 -enamines [5]. The absorption bands at 3058 cm^{-1} and 2810 cm^{-1} in the IR spectra are ascribed to the valence vibrations of the C–H and N–H bonds. The double absorption band of the valence vibrations of the C = C bond at 1675 and 1648 cm^{-1} and the absorption bands ascribed to the unsymmetrical deformation vibrations of the =C–H bond, with maxima at 889 and 827 cm^{-1}, indicate the presence of two types of Δ^2 -enamines, 1,2-dimethyl-Δ^2-piperidine (X) and 1-methyl-4,5,6,7-tetrahydroazepine (XI) [6].

The constants, retention times, and PMR and IR spectra of the compound corresponding to peak 3 in the chromatogram were in agreement with the characteristics of an authentic sample of 1-methyl-2- hydroxy-piperidine (VII).

The compound corresponding to peak 4 in the chromatogram could not be isolated in pure form since it is partially dehydrated to enamine X under the conditions of alkaline, preparative column gas chromatography at a separation temperatures of 150 deg. Two peaks are visible on the chromatogram of the compound after preparative isolation. The retention time of the first coincided with the retention time of 1,2-dimethyl Δ^2-piperideine, while that of the second corresponded to a component of the four reaction products.

In addition to the signals from the protons of enamine X, the PMR spectrum of the mixture formed by dehydration contained signals from the portons of a basic compound. In addition to the characteristic absorption bands of enamine X, absorption bands of aminoketone IX were also observed in the IR spectrum (see Experimental).

On the basis of these data and the structure of X, formed during dehydration, aminoketone structure IX was assigned to component 4.

Measurement of the areas of the signals in the chromatogram of the reaction products (Fig. 1) made it possible to determine their ratios: 26% 1,2-dimethyl-Δ^2-piperidine (X), 9% 1-methyl-4,5,6,7-tetrahydroazepine (VI), 49% 1-methyl-2-hydroxymethylpiperidine (VII), and 16% 6-methylamino-2-hexanone (IX).

EXPERIMENTAL

1-Methyl-2-aminomethylpiperidine. A solution of 5 g (0.05 mole) of the nitrile of picolinic acid in 10 ml of absolute methanol was mixed with 10 g (0.1 mole) of freshly prepared frozen methyl bromide, and the mixture was heated in an autoclave at 110 deg for 2 h. The excess methyl bromide was removed in vacuo to give 9.4 g (98%) of impure reaction product with mp 195-199 deg.

The methyl bromide adduct (9.4 g) was dissolved in 20 ml of water, and the solution was refluxed with 0.5 g of activated charcoal. The solution was filtered, 11 ml (0.1 mole) of hydrochloric acid (sp. gr. 1.19) was added to the filtrate, and the mixture was placed in an apparatus for hydrogenation at 2-3 atm abs. The hydrogenation was carried out in the presence of 0.2 g of PtO_2. Hydrogen absorption was quantitative (5.3 liter). The catalyst was removed by filtration, and the solution was neutralized, saturated with potassium carbonate, and extracted with four 10-ml portions of ether. The ether solution was dried with fused potassium carbonate and distilled to give 5.8 g (95%) of 1-methyl-2-aminomethylpiperidine with bp 68-69 deg (10 mm), n_D^{20} 1.4731, and d_4^{20} 0.9102. Found: MR_D 39.54. $C_7H_{16}N_2$. Calc.: MR_D 39.74 [7]. According to gas-liquid chromatography, the compound contains less than 0.5% 1-methyl-3-aminomethylpiperidine.

PMR spectrum: singlet at 0.74 ppm (amino protons); multiplet at 1.30-1.62 ppm (protons of the β- and γ-methylene groups and the axial proton of the α-methylene group; singlet at 2.04 ppm (N-methyl group protons); doublet at 2.42 ppm ($J = 4.9$ Hz) (aminomethyl group protons); weak doublet at 2.78 ppm ($J = 10$ Hz) (equatorial proton of the α-methylene group); singlet at 3.18 ppm (methine group proton).

1-Methyl-2-hydroxymethylpiperidine. A solution of 4.7 g (0.03 mole) of methyl N-methylpicolinate in 50 ml of absolute ether was added dropwise and slowly with continuous stirring to an ice-cooled suspension of 1.5 g (0.04 mole) of lithium aluminum hydride in 200 ml of ether. At the end of the addition, the reaction mass was allowed to stand for 12 h at room temperature and then refluxed for 2 h. The excess lithium aluminum hydride was carefully decomposed with 2 ml of water until hydrogen evolution ceased. The ether solution was filtered, and the solid residue was washed twice with ether (25-ml portions), dried with fused potassium carbonate, and distilled to give 3.45 g (88%) of 1-methyl-2-hydroxymethylpiperidine with 87-88 deg (8.5 mm) [7], n_D^{20} 1.4795, and d_4^{20} 0.9755. Found: MR_D 37.62. $C_7H_{15}NO$. Calc.: MR_D 37.79.

PMR spectrum: multiplet at 1.22-1.76 ppm (protons of the β-, β'-, and γ-methylene groups and axial protons of the α-methylene groups); singlet at 2.11 ppm (N-methyl group protons); doublet at 2.76 ppm ($J_{a,e} = 10$ Hz) (equatorial proton of the α-methylene group), doublet at 3.48 ppm ($J = 6$ Hz) (methoxy group protons); singlet at 4.05 ppm (hydroxyl group proton).

1,2-Dimethylpiperidine. The synthesis was carried out via a method similar to that used to prepare 1,3-dimethylpiperidine [1]. A combination of 25 g (0.27 mole) of α-picoline and 70 g (0.75 mole) of methyl bromide gave, after reduction, 21 g (69%) of 1,2-dimethylpiperidine with bp 127-128 deg (754 mm) n_D^{20} 1.4438, and d_4^{20} 0.8221 [8.9]. Found: MR_D 36.59. $C_7H_{15}N$. Calc.: MR_D 36.27. PMR spectrum: doublet at 0.92 ppm ($J = 3.8$ Hz) (C-methyl group protons): multiplet at 1.22-1.72 ppm (protons of the β-, β'-, and γ-methylene groups and axial proton of the α-methylene group); singlet at 2.15 ppm (N-methyl group protons); doublet at 2.78 ppm ($J_{a,e} = 9.7$ Hz) (equatorial proton of the α-methylene group).

Deamination of 1-Methyl-2-Aminomethylpiperidine. A 10% solution of phosphoric acid was added to a solution of 5.1 g (0.04 mole) of the amine in 25 ml of water until the pH was 5.5. A 10% solution of sodium nitrate [40 ml (0.06 mole)] was added during 20 min with vigorous stirring to the salt at 0 deg while maintaining the temperature at precisely 0 deg. The reaction mass was stirred for 2h at 0 deg and allowed to stand at 20 deg for 12 h. It was then heated to 60 deg for 10 min and cooled. The reaction products after neutralization and saturation of the solution with potassium carbonate were extracted with three 15-ml portions of ether. Distillation of the ether extract yielded a fraction with unsaturated compounds: (5.1% of the theoretical yield) with bp 99-107 deg (13 mm) and a fraction with alcohols (21%) with bp 101-110 deg (8 mm). The overall yield was 26.1%. The ether extract of the reaction products had the following composition according to gas-liquid chromatography: 26% 1,2-dimethyl-Δ^2-piperideine, 9% 1-methyl-4,5,6,7-tetrahydroazepine, 49% 1-methyl-2-hydroxymethylpiperidine, and 16% 6-aminomethyl-2-hexanone.

Two components were obtained by separation of the "alcohol" fraction on the preparative column of a gas-liquid chromatograph. The first was identified as 1-methyl-2-hydroxymethylpiperidine. The IR spectra of the product isolated from the reaction and an authentic sample of the alcohol were identical: 3440 cm^{-1}(ν_{OH}), 1462 cm^{-1} (δ_{CH}), 1400 cm^{-1} (δ_{OH}), 1375 cm^{-1} (δ_{CH_3}), and 1203 and 1115 cm^{-1}(ν_{C-O}). Their melting points, MR_D values, retention times (4.5 min), and PMR spectra were also identical.

The second component was 6-aminomethyl-2-hexanone (retention time (10.6 min). As already noted, the control chromatograph indicated that this compound is partially dehydrated to 1,2-dimethyl-Δ^2-piperidine during preparative isolation. The singlets at 2.60 and 2.75 ppm in the PMR spectrum of the mixture formed in the process belong to the protons of the C- and N-methyl groups of the enamine, while the singlets at 1.66 and 2.15 ppm belong to the protons of the C- and N-methyl groups of the amino ketones; the signals of the β- and γ- methylene protons of both compounds form a common multiplet (approximately six lines) centered at 1.15 ppm while the signals of the α-methylene protons ($C-CH_2-X$) at 1.85-2.65 ppm give two poorly resolved multiplets. The absorption maxima in the IR spectra at 1640, 1675, and 3060 cm^{-1} are ascribed to the valence vibrations of the C=C and =C−H groups in the enamine. The absorption at 3330 and 1715 cm^{-1} correspond to the valence vibrations of the N−H and C=O groups in the amino ketone.

The fraction containing the unsaturated compounds was composed of 74% 1,2-dimethyl-Δ^2piperideine (retention time 16 min) and 26% 1-methyl-4,5,6,7-tetrahydroazepine (retention time 21 min at a column temperature of 100 deg and a gas-carrier flowrate of 20 ml/min).

Hydrogenation [1] of the mixture of unsaturated compounds gave, according to gas-liquid chromatography, a mixture consisting of 1,2-dimethylpiperidine (74%) and 1-methylhydroazepine (26%). The retention times of the compound obtained coincided with the retention times of authentic samples and were 6.0 and 8.6 min at a column temperature of 100 deg and a gas-carrier flowrate of 20 ml/min.

LITERATURE CITED

1. L. B. Dmitriev, I. I. Grandberg, and V. A. Moskalenko, Izv. TSKhA, 2, 195 (1969).
2. L. B. Dmitriev, I. I. Grandberg, and V. A. Moskalenko, Khim. Geterotsikl. Soedin. (in press).
3. M. Tiffeneau, R. Weill, and B. Tchoubar, Compt. Rend., 205, 54 (1937).
4. M. Mousseron, R. Jacquier, and J. Ajullien, Bull. Soc. Chim. France, 89 (1951).
5. N. I. Lenard and D. M. Locke, J. Am. Chem. Soc., 77, 437 (1955).
6. M. Holik and A. Tesorova, Coll., 32, 1730 (1967).
7. A. A. Brode and C. Bremer, J. Am. Chem. Soc., 56, 993 (1934).
8. A. Lipp, Ann., 286, 225 (1896).
9. W. Leithe, Ber., 63, 805 (1930).